Upon entry of this amendment claims 14 through 28 are pending in the application. Claims 1-13 have been cancelled, and claims 15 through 28 have been added, and claim 14 has been amended to more clearly describe the invention. Support for the amendments to claim 14 is found generally within the specification; in Figure 17; from page 60, line 6 to page 61, line 11; at page 68 lines 14-16; and at page 79, lines 21-35. Support for claims 15 through 19 and claims 23 through 26 is found generally within the specification and in canceled claims 2 through 13. Support for claim 23 is found generally within the specification; in the specification between pages 101 through 122, and in particular at page 110. Support for claim 20 and claim 27 is found generally within the specification and from page 26, line 31 to page 27, line 25. Support for claim 21 and claim 28 is found generally within the specification and at page 56, lines 22 through 31.

Thus, the amendments to the claims are fully supported by the application as filed, add no new matter, and should not be construed as limiting the appropriate scope of protection under the doctrine of equivalents.

Information Disclosure Statement

The Examiner has requested the relationship of the applications listed on the 1449 of Paper No. 19 to the instant application. The WO 96/30392 publication is an application directed to a process for the production of combinatorial compound libraries assigned to Ciba-Geigy AG. The WO 97/46704 publication is an application directed to a method for nucleic acid sequence analysis based on the ligation of one or more sets of encoded adaptors to the terminus of a target polynucleotide assigned to Lynx Therapeutics and is part of the patent family that resulted in U.S. Patent No. 6,280,935. The WO 98/31836 publication is an application concerning methods for detection or quantification of nucleic acid sequences. The WO 99/64867 publication is an application for the assay of a multiplicity of samples using carrier beads and is assigned to Amersham Pharmacia Biotech UK. The WO 00/71992 publication is an application directed to a

method and apparatus for retaining and presenting a microsphere array to solutions and/or optical imaging systems. It is assigned to Illumina, as is the instant application.

Rejections under 35 U.S.C. §102(e)

The Examiner has alleged that claims 1-9, 11, 13 and 14 are anticipated by Macevicz (U.S. Patent No. 6,280,935, filed June 4, 1998). The Applicant respectfully submits that the rejection no longer applies to the claim as Macevicz does not describe all of the limitations in amended claim 14 and new claims 15 through 28.

Rejections under 35 U.S.C. §103

The Examiner has rejected claims 10 and 12 as allegedly obvious over Macevicz (U.S. Patent No. 6,280,935, filed June 4, 1998) in view of Walt et al. (U.S. Patent No. 6,327,410, filed September 11, 1998). Applicants respectfully traverse the Examiner's rejection. The Examiner has failed to establish a prima facie case of obviousness. The Examiner has not provided any suggestion in either reference to provide motivation to combine the references. However, in the interest of speeding prosecution, Applicants have cancelled claims 1-13 and amended claim 14. Applicants respectfully submit that the rejection no longer applies to claim 14 as amended. Neither Macevicz nor Walt is seen to teach or is seen to suggest the extension step prior to the ligation step of claim 14.

The Examiner has rejected claims 1-14 as allegedly obvious over Barany et al. (U.S. Patent No. 6,027,889 filed May 28, 1997) in view of Walt et al. (U.S. Patent No. 6,023,540, filed May 14, 1997). Applicants respectfully traverse the Examiner's rejection. The Examiner has failed to establish a prima facie case of obviousness. The Examiner has not provided any suggestion in either reference to provide motivation to combine the references. However, in the interest of speeding prosecution, Applicants have cancelled claims 1-13 and amended claim 14. Applicants respectfully submit that the rejection no longer applies to claim 14 as amended.

Rejections for Double Patenting

Claims 1-14 stand provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-14 of copending Application No. 09/556,463.

Claims 1-14 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 and 15-16 of copending Application No. 09/535,854 and copending Application No. 09/513,362.

Applicants respectfully request that these rejections be held in abeyance until allowable subject matter is identified. At that time, Applicants will submit a terminal disclaimer to overcome the rejection.

CONCLUSION

All of the above changes are cosmetic and none raise any issue of patentability. Both before and after the above changes, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 U.S.C. 101 et seq. The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to embrace all equivalents. Accordingly, under no circumstances whatsoever may these claims be interpreted as:

having been altered in any way for any reason related to patentability;
having been narrowed;
a concession that the invention as patented does not reach as far as the original, unamended claim;
a surrender of any subject matter as a condition of receiving a patent; and/or,
estopping applicants from asserting infringement against every equivalent, whether now known or later developed, foreseen or unforeseen;

Applicants also emphasize that the decision to address the Examiner's suggestions via claim amendment with the understandings set forth above is not in any way intended to avoid the "gatekeeping" role of the PTO with regard to the examination and issuance of valid patents for patentable inventions.

It is believed that all claims are now in condition for allowance. Notification to that effect is respectfully requested. If it is believed that prosecution may be furthered thereby, the Examiner is invited to contact Applicant's undersigned representative to discuss the same.

No additional fee is believed to be due with the filing of this Amendment, but if applicant is in error, the Commissioner is hereby authorized to debit deposit account number 50-1273 for any fee due.

Respectfully submitted,

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Dated: 11/26/02

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Amended Claim with Changes Noted

14. (Twice Amended) A method of detecting a target nucleic acid sequence comprising:

a) hybridizing a first primer to a first portion of a target sequence, wherein said first primer further comprises an adapter sequence;

b) hybridizing a second primer to a second portion of said target sequence wherein said first portion of said target sequence and said second portion of said target sequence are not adjacent;

c) extending either said first primer or said second primer towards the other;

[c]d) ligating said first and second primers together to form a modified primer;

[d]e) contacting said adapter sequence of said modified primer or its complement with an array comprising:

i) a substrate with a surface comprising discrete sites; and

ii) a population of microspheres comprising at least a first subpopulation comprising a first nucleic acid capture probe, such that said first capture probe and an amplification product of said modified primer form a hybridization complex; [that hybridizes to said adapter sequence,] wherein said microspheres are distributed on said surface; and

[e]f) detecting the presence of said modified primer, to thereby detect said nucleic acid sequence.

Summary of Pending Claims Following Entry of the Amendments

14. A method of detecting a target nucleic acid sequence comprising:

a) hybridizing a first primer to a first portion of a target sequence, wherein said first primer further comprises an adapter sequence;

b) hybridizing a second primer to a second portion of said target sequence wherein said first portion of said target sequence and said second portion of said target sequence are not adjacent;

c) extending either said first primer or said second primer towards the other;

d) ligating said first and second primers together to form a modified primer;

e) contacting said adapter sequence of said modified primer or its complement with an array comprising:

i) a substrate with a surface comprising discrete sites; and

ii) a population of microspheres comprising at least a first subpopulation comprising a first nucleic acid capture probe, such that said first capture probe and an amplification product of said modified primer form a hybridization complex; wherein said microspheres are distributed on said surface; and

f) detecting the presence of said modified primer, to thereby detect said nucleic acid sequence.

15. The method according to claim 14 further comprising:

a) hybridizing a third primer to a first portion of a second target sequence, wherein said third primer further comprises a second adapter sequence;

b) hybridizing a fourth primer to a second portion of said second target sequence wherein said first portion of said second target sequence and said second portion of said second target sequence are not adjacent;

c) extending either said third primer or said fourth primer towards the other;

d) ligating said third and fourth primers together to form a second modified primer;

e) contacting said second modified primer or its complement with said array, wherein said population of microspheres comprises at least a second subpopulation comprising a second capture probe, such that said second capture probe and said second modified

primer or its amplification product form a hybridization complex comprising said second capture probe, said second adapter sequence; and

f) detecting the presence of said second modified primer.

16. The method according to claim 14, wherein said modified primer is amplified.

17. The method according to claim 14, wherein said wherein said detecting is done by hybridizing a labeled probe to said ligated first and second primers.

18. The method according to claim 14, wherein said substrate is a fiber optic bundle.

19. The method according to claim 14, wherein said discrete sites comprise wells.

20. The method according to claim 14, wherein said wherein said detecting is done by labeling amplification products from said ligated first and second primers.

21. The method according to claim 14, wherein said wherein either said first primer or said second primer is an allele specific primer.

22. A method for simultaneously detecting at least sixteen target nucleic acid sequences comprising:

a) hybridizing a first primer of at least sixteen pairs of primers to a first portion of at least sixteen target sequences, wherein each primer pair is specific for a different sequence, wherein said first primer further comprises an adapter sequence;

b) hybridizing a second primer of said primer pairs to a second portion of said target sequences;

c) ligating said first and second primers together to form a modified primer;

d) contacting said adapter sequence of said modified primer or its complement with an array comprising:

i) a substrate with a surface comprising discrete sites; and

ii) a population of microspheres comprising at least a first subpopulation comprising a first capture probe, such that said first capture probe and an amplification product of said modified primer form a hybridization complex; wherein said microspheres are distributed on said surface; and

e) detecting the presence of said modified primer.

23. The method according to claim 22, wherein said modified primers are amplified.

24. The method according to claim 22, wherein said wherein said detecting is done by hybridizing a labeled probe to said ligated first and second primers.

25. The method according to claim 22, wherein said substrate is a fiber optic bundle.

26. The method according to claim 22, wherein said discrete sites comprise wells.

27. The method according to claim 22, wherein said wherein said detecting is done by labeling amplification products from said ligated first and second primers.

28. The method according to claim 22, wherein said wherein one of said first primer or said second primer of each primer pair is an allele specific primer.